2. SYNOPSIS

Title of Study: A Parallel Group Double-Blind Randomized Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Frequent Episodic Migraines

Investigators: [redacted]

Study Sites: This study was conducted at 84 study sites by 82 investigators; 79 sites in the United States and 5 sites in the Republic of Georgia. Two investigators conducted the research at 2 sites each.

Publication(s) (Reference): None

Study Period: 30 Sep 2015 (First subject first visit) to 14 Dec 2017 (Last subject last visit)

Phase of Development: 3

Objectives: The primary study objective was to evaluate the efficacy of repeat doses of ALD403 administered by intravenous (IV) infusion compared to placebo in subjects with frequent episodic migraine (FEM). The secondary study objectives were the following: 1) to evaluate the safety of repeat doses of ALD403 administered IV compared to placebo in subjects with FEM and 2) to evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered IV to subjects with FEM.

Methodology: This was a Phase 3, parallel group, double-blind, randomized, placebo-controlled study. Eligible subjects were randomly assigned into 1 of 3 ALD403 dose levels (30 mg, 100 mg, and 300 mg) or placebo in a 1:1:1:1 ratio. Randomization was stratified by migraine days during screening (≤9 days versus >9 days). Subjects were allocated equally to each treatment group.

The total duration of the study was 60 weeks, with 12 scheduled visits. The visits occurred at screening, on Day 0 and at Weeks 4, 8, 12, 16, 20, 24, 28, 36, 48, and 56. The 56 weeks were

divided into 2 periods: a blinded analyses period of 24-week safety and efficacy period (Weeks 1-24) and a long-term safety period (Weeks 25-56).

Subjects were issued an eDiary to track headache and migraine episodes, and followed for 4 weeks after the screening visit to confirm relevant eligibility criteria and establish baseline values. Eligible subjects were randomly assigned and treated with study drug or placebo on Day 0, which was between 29 to 35 days after the screening visit. Subjects completed the eDiary from screening through Week 48. The subjects who were randomly assigned and dosed with study drug were to continue in the study through Week 56.

Study drug included 4 total IV infusions of ALD403 or placebo. A single IV infusion occurred on Days 0, 84 (Week 12), 168 (Week 24), and 252 (Week 36) with 20 weeks of postdose follow-up through Week 56.

Number of Subjects: There were 888 randomized and treated subjects in this study.

Diagnosis and Main Criteria for Inclusion: Males and females 18 to 75 years of age (inclusive), first diagnosed with migraines at ≤50 years of age, history of migraine for ≥12 months at a frequency of ≤14 headache days of which at least 4 had to be migraine days (migraine days counted as headache days) in each 28-day period in the 3 months before screening, and no regular use (greater than 7 days) of prophylactic headache medication within 2 months before screening. Frequent episodic migraine (FEM) was an eligibility requirement for this study, which was defined as ≥4 and ≤14 headache days of which at least 4 had to be migraine days during the 28-day screening period as recorded in the eDiary. Subjects were also required to meet eDiary compliance criteria of at least 25 of 28 days completed during the screening period.

Test Product, Dose and Mode of Administration, Batch Number(s): ALD403 injection, 100 mg/mL (1.0 mL per vial), was presented in 2-mL Type I glass vials as a single-use, preservative-free solution for IV administration. ALD403 was formulated at a concentration of 100 mg/mL with a pH of 5.8. The following ALD403 lot numbers were used: 1-FIN-2200, 1-FIN-2201, 1-FIN-2348, 1-FIN-2349, and 1-FIN-2350. Those subjects randomized to study drug received an IV infusion of ALD403 injection in 100 mL of 0.9% saline. ALD403 was administered as an IV infusion over a period of 1 hour at doses of 30, 100, and 300 mg once every 12 weeks.

Placebo (lot number 1-FIN-2230) was supplied as a single-use preservative-free solution in 2-mL Type I glass vials formulated with the same excipients as ALD403, without the active ingredient. Those subjects randomized to placebo received an IV infusion of placebo in 100 mL of 0.9% saline, administered as an IV infusion over a period of 1 hour once every 12 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number(s): None.

Duration of Treatment: A single dose of ALD403 or placebo was given on 4 separate occasions with doses given approximately 12 weeks apart. The total study participation period was 60 weeks, which included a 4-week screening period, randomization and the start of treatment on Day 0, further dosing at Weeks 12, 24, and 36, and 20 weeks of postdose follow-up, ending at Week 56.

Criteria for Evaluation:

Primary Endpoint: The primary efficacy endpoint was the change in frequency of migraine days (Weeks 1-12).

Key Secondary Efficacy Endpoints: The key secondary endpoints were the following:

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rate (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing.

Other Secondary Efficacy Endpoints: The other secondary efficacy endpoints were the following:

- Change in acute migraine medication days (Weeks 1-12)
- Headaches/migraines with acute medication usage
- 100% migraine responder rates (Weeks 1-12)
- Short-Form Health Survey (SF-36)
- Health-Related Quality of Life (EQ-5D-5L)
- Allodynia Symptom Checklist-12 (ASC-12)
- Brush (dynamic mechanical) Allodynia
- Migraine responder rates for time periods other than Weeks 1-12
- Change in frequency of migraine days between baseline and time periods other than Weeks 1-12
- Headache responder rates

- Change in the frequency of headache days
- Percent change in migraine/headache days
- Time to first migraine after dosing
- Migraine/headache hours
- Migraine/headaches with severe intensity

Tertiary and Exploratory Efficacy Endpoints: The tertiary and exploratory efficacy endpoints were the following:

- Headache episodes/migraine attacks
- Migraine/headache characteristics
- Migraine/headache with type of acute medication usage
- Migraine attack/headache episode average length

Safety Endpoints: The safety endpoints were the following:

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in clinical laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- Suicidal ideation and behavior as measured by the Columbia-suicide severity rating scale (C-SSRS)

Pharmacokinetic Endpoints: The pharmacokinetic (PK) analysis included evaluations of individual concentration-time profiles for free ALD403. When data permitted, PK parameters for ALD403 including C_{max}, C_{min}, $C_{trough\ Day\ 84}$, $C_{trough\ Day\ 168}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}2016}$ (or $AUC_{0\text{-}\tau}$ after multiple doses), ARAUC, and ARC_{max} were calculated.

Immunogenicity Endpoints: The immunogenicity endpoints were the following:

- Development of anti-ALD403 antibodies
- Characterization of anti-ALD403 antibodies for neutralizing activity and epitope specificity of the ADA response

Statistical Methods: The analysis populations included the full analysis population, the safety population and the pharmacokinetic population. The full analysis population comprised all randomized subjects who received study drug or placebo. The safety population included all subjects who received study drug or placebo. The PK population included all subjects who had at least 1 reportable plasma concentration of ALD403.

Efficacy Endpoints: A serial procedure was used to account for multiplicity of dose level for the primary endpoint and the secondary endpoints. If the 300 mg versus placebo comparison for the primary endpoint was significant, testing continued on a subset of the key secondary endpoints for 300 mg (Weeks 1-4, 75% responder endpoint followed by the Weeks 1-12, 75% responder endpoint, and the Weeks 1-12, 50% responder endpoint). The procedure was then applied to the primary endpoint for the 100-mg group, and subsequently to the same subset of key secondary endpoints as tested for the 300-mg dose. The procedure then moved on to the remaining key secondary endpoints for 300 mg and 100 mg. The 30-mg group was to be tested only if all of the preceding primary and secondary endpoints had reached statistical significance.

For all efficacy endpoints, the full analysis population was used and endpoints were calculated from migraine/headache episodes that were self-reported by subjects in the eDiary. For analysis of migraine/headache days, the number of migraine/headache days, change from baseline and the percent change by 4-, 12-, and 24-week intervals and treatment group were summarized in tables. The treatment difference and associated confidence interval were provided. The analysis of covariance (ANCOVA) model, controlling for the effects of baseline migraine days (a stratification factor for randomization), was used to calculate the estimated treatment difference from placebo, the change from baseline and the associated confidence intervals for the 12- and 24-week intervals. The ANCOVA model was used to test for a treatment difference in the primary endpoint change from baseline in migraine days for Weeks 1-12.

For responder rates, the number of subjects who were responders and the rate (full analysis population as the denominator) were summarized for each treatment group and in each 4-, 12-, and 24-week interval. The difference in rates and associated confidence interval was produced. These confidence intervals were calculated based upon the normal approximation for 2 independent proportions. Stratification was not used for these intervals.

Summary tables including confidence intervals for the treatment difference for the 4, 12, and 24-week time intervals were produced for the remaining headache and migraine secondary endpoints (headache and migraine hours, headaches and migraines with severe intensity, and headaches and migraines with acute medication usage). The secondary endpoints were summarized with descriptive statistics by timepoint. These summary measures were based upon the observed results and where appropriate the change from baseline results.

For other efficacy endpoints (SF-36, EQ-5D-5L, ASC-12, brush allodynia), summaries at each scheduled visit by treatment group were produced using descriptive statistics.

Pharmacokinetic Endpoints: The PK analysis included evaluations of concentration-time profiles for free ALD403 at the following times: predose on Day 0, and Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 56. The concentrations of free ALD403 were listed and summarized by timepoint, dose group, and group identifier, and descriptive statistics were provided.

All ALD403 PK calculations were performed using actual timepoints calculated relative to the start of IV infusion of ALD403. Assuming there was a sufficient number of measurable ALD403 concentrations, the following PK parameters were determined using noncompartmental (NCA) methods with WinNonlin® (v.7.0) based on the individual ALD403 concentration-time data for each subject in the PK population:

Parameter	Description
$AUC_{0\text{-last}}$	Area under the ALD403 concentration-time curve from the time of dosing (0 h) to the time of the last quantifiable concentration following dose administration, calculated by the linear trapezoidal rule for ascending concentrations and by the log-linear trapezoidal rule for descending concentrations (linear up-log down trapezoidal method).
$AUC_{0\text{-}2016}$ (or $AUC_{0\text{-}\tau}$ after multiple doses)	Area under the ALD403 concentration-time curve from the time of dosing (0 h) to the time of the last quantifiable concentration following dose administration, calculated by the linear trapezoidal rule for ascending concentrations and by the log-linear trapezoidal rule for descending concentrations (linear up-log down trapezoidal method). After multiple dose, AUC0-2016 may also be labelled as AUC0-τ, the area under the plasma concentration-time curve from time zero to tau, where tau is the dosing interval (ie, 2016 h [84 days]).
C_{max}	Maximum observed ALD403 concentration from the time of dosing (0 h) to the time of the last quantifiable ALD403 concentration following dose administration.
t_{max}	Time of maximum observed ALD403 concentration (postdose).
C_{min}	Minimum observed ALD403 concentration from the time of dosing (0 h) to the time of the last quantifiable ALD403 concentration following dose administration.
t_{min}	Time of minimum observed ALD403 concentration (postdose).
$C_{trough\ Day\ 84}$	The observed ALD403 concentration at the end of the dosing interval (τ = 12 weeks) collected following the first IV Infusions of ALD403 (Day 0).
$C_{trough\ Day\ 168}$	The observed ALD403 at the end of the dosing interval (τ = 12 weeks) collected following the second IV Infusions of ALD403 (Week 12).
ARAUC	Accumulation ratio (based on AUC), calculated as: $AUC_{0\text{-}\tau}$ Day 84 (Week 12) /$AUC_{0\text{-}2016}$ Day 0 (Week 1)
ARC_{max}	Accumulation ratio (based on C_{max}), calculated as: C_{max} Day 84 (Week 12) /C_{max} Day 0 (Week 1)

Safety Endpoints: Adverse events (AEs) were collected from the time of informed consent through the final subject visit. A treatment-emergent AE (TEAE) was an AE with a start date on or after the date of the first study drug dose. The incidences of all AEs and TEAEs were

tabulated by treatment received. These AEs were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1. For incidence reporting, if a subject reported more than 1 AE that was coded to the same preferred term/system organ class, the subject was counted only once for that specific preferred term/system organ class.

An overview of AEs, which included subject incidence of TEAEs, study drug-related TEAEs, serious TEAEs, TEAEs leading to treatment withdrawal, TEAEs leading to treatment interruption, TEAEs leading to discontinuation and deaths were presented. The subject incidence of TEAEs and study drug-related TEAEs were summarized by system organ class and preferred term. Treatment-emergent AEs were also summarized in a table by severity. For TEAEs presented by severity, the worst severity for each event during the clinical study was presented for each subject. All AEs were presented as a listing by subject.

All SAEs were listed and summarized in a similar manner to TEAEs. A listing of deaths was presented.

Treatment-emergent adverse events of special interest (AESIs) included the following: hypersensitivity and anaphylactic events, events associated with C-SSRS, cardiovascular events, nervous system disorders, hepatic events, and events associated with study drug infusion. The AESIs were summarized and listed in the following categories: system organ class (SOC) and preferred term (PT); SOC, PT, and maximum severity; SOC, PT, and relationship to study drug; led to infusion interruption by SOC and PT; action taken of study drug discontinuation by SOC and PT; and assessed as serious by SOC and PT.

Immunogenicity endpoints: Immunogenicity analyses were conducted using the safety population.

The number and percent of subjects with pre-existing antibodies at baseline, and subjects who developed anti-drug antibodies to ALD403 during the study were summarized at each scheduled visit as well as the overall incidence of ADA positive subjects in the same table. Denominators for percentages for each were the total number of results available for the specified visit, and the total number of results for the overall incidence. All the immunogenicity data were presented in by-subject listings.

Results:

Efficacy Results: A total of 898 subjects were randomized. A total of 888 subjects (98.9%) received treatment and were included in the safety population and full analysis population. A total of 10 subjects (1.1%) were randomized but not dosed.

Overall, subject demographics, migraine history, migraine and headache characteristics across treatment groups were generally well-balanced and any minor differences observed were not considered to be clinically relevant. In addition, the overall medical and surgical

history for subjects across treatment groups was generally well-balanced at the SOC level and there were no differences identified at the PT level that were considered to be clinically relevant.

Concomitant medication use was well-balanced across treatment groups at the Drug Class level. The regular use of prophylactic medications for migraine (ie, any preventive medication or supplement with evidence of efficacy from at least 1 placebo-controlled trial) was restricted from 2 months prior to the screening visit through Week 24 of the study. Therefore, overall use of migraine preventive treatment in the study was low.

Based on the decision rule, the results for the primary endpoint (the change in frequency of migraine days for Weeks 1-12), and key secondary endpoints (such as 75% migraine responder rate over Weeks 1-4, 75% and 50% migraine responder rates over Weeks 1-12) for the ALD403 300-mg group were statistically significant per the prespecified statistical testing hierarchy. The primary endpoint and 75% migraine responder rate over Weeks 1-4 were statistically significant for the ALD403 100-mg dose; however, the 75% migraine responder rate over Weeks 1-12 was not statistically significant. The remaining key secondary endpoints in the ALD403 300-mg and 100-mg groups were not statistically significant despite unadjusted p-values being <5%, due to the decision rules of multiple testing. The unadjusted p-values in the 30-mg group for the primary endpoint and key secondary responder rates were <5% and were not statistically significant results, per the decision rules of multiple testing.

For the key secondary endpoint assessing the percentage of subjects with a migraine on the day after dosing (Day 1), results for the ALD403 300-mg and 100-mg groups were clinically meaningful and nominally significant (unadjusted p-values being < 5%) compared with placebo.

For the average migraine days change from baseline in 4-week intervals through 48 weeks, results showed consistently reduced average migraine days in all the ALD403 treatment groups compared with placebo. The therapeutic effect was consistently maintained in the ALD403 300-mg group across all dosing intervals.

For the 50% and 75% migraine responder rates by 4-week intervals and treatment, the overall number (%) of subjects with a 50% or greater and 75% or greater reduction in migraines from Weeks 1-48 was consistently higher in the ALD403 treatment groups than in the placebo group. For the 75% migraine responder rate (Weeks 1-4), the common odds ratios of the ALD403 300-mg, ALD403 100-mg and ALD403 30-mg groups, over placebo were estimated as 1.817 (95% CI: 1.179, 2.802), 1.752 (95% CI: 1.134, 2.705) and 1.694 (95% CI: 1.096, 2.618), respectively. For the 75% migraine responder rate (Weeks 1-12), the common odds ratios of the ALD403 300-mg, ALD403 100-mg and ALD403 30-mg groups, over placebo were estimated as 2.179 (95% CI: 1.379, 3.443), 1.470 (95% CI: 0.912, 2.368) and 1.686 (95% CI: 1.057, 2.689), respectively. For the 50% responder rate (Weeks 1-12) common odds ratios of the ALD403 300-mg, ALD403 100-mg and ALD403 30-mg groups,

over placebo were estimated as 2.158 (95% CI: 1.476, 3.155), 1.662 (95% CI: 1.138, 2.427) and 1.691 (95% CI: 1.159, 2.468), respectively. The lower confidence intervals of odds ratio in the 300-mg and 30-mg dose levels of ALD403 arms excluded 1, which was consistent with the observed p-value for this endpoint.

The ALD403 300-mg group was associated with greater 100% migraine responder rates over each 4-week interval compared with placebo over Weeks 1-12. Results for the ALD403 30-mg and 100-mg group were less consistent over the same 12-week period.

Mean acute migraine medication days was low at baseline and was reduced over Weeks 1-12 in all treatment groups. The reductions in acute migraine medication days from baseline were numerically greater in the ALD403 treatment groups with nominally statistically significant reductions in the ALD403 300-mg and ALD403 100-mg groups compared to the placebo group.

Reductions in headache days were observed in all treatment groups. The changes observed for headache days were slightly larger than the changes seen for migraine days. In the ALD403 groups, the reductions in headache days from baseline were numerically greater than those observed in the placebo group. The percent change from baseline was generally consistent among the ALD403 treatment groups. Headache responder rates were similar to migraine responder rates except for the 100% headache responder rates, where results were lower than the 100% migraine responder rates.

Over Weeks 1-12, the percent of severe migraines were reduced from baseline by approximately 9% to 12% in the ALD403 treatment groups, compared with a reduction from baseline of approximately 8% in the placebo group. Results for the reduction in migraine and headache hours were similar.

The ALD403 300-mg group showed consistent reductions from baseline in monthly migraine days when compared with placebo across all clinically important subgroups. Due to small sample size of certain subgroups, such as male subjects, subjects of black race and subjects of other races, wider CIs were observed. These subgroups had point estimates favoring ALD403 300 mg; however, the reduction from baseline in monthly migraine days was similar to the placebo group. Overall, the reductions from baseline in the ALD403 300-mg group were more robust and consistent across the analyzed subgroups compared to the ALD403 100-mg group.

Pharmacokinetic Results: After the single dose administration of ALD403 at 3 dose levels (30 mg, 100 mg, and 300 mg), mean plasma ALD403 $AUC_{0\text{-last}}$ and $AUC_{0\text{-2016}}$ increased proportionally with dose and ranged from 3617.4 to 32745.5 h*µg/mL and from 3779.4 to 33289.0 h*µg/mL for $AUC_{0\text{-last}}$ and $AUC_{0\text{-2016}}$, respectively. Mean plasma ALD403 C_{max} also increased proportionally with dose and ranged from 3.615 to 30.58 µg/mL. Mean C_{trough} was proportional to dose and ranged from 0.8229 to 8.288 µg/mL. Median t_{max} ranged from 671.68 to 672.46 hours after single dose administration in subjects with FEM, and was

independent of dose. Intersubject variability of $AUC_{0\text{-}2016}$, $AUC_{0\text{-last}}$, and C_{max} ranged from 36.1 to 83.7%.

After multiple dose administrations, mean plasma ALD403 $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\tau}$ increased proportionally with dose and ranged from 4185.4 to 40592.6 h*µg/mL and from 4312.6 to 41715.1 h*µg/mL for $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\tau}$, respectively. Mean plasma ALD403 C_{max} also increased proportionally with dose and ranged from 4.023 to 36.72 µg/mL. Mean C_{trough} increased proportionally over the dose range and ranged from 1.011 to 9.576 µg/mL. Median t_{max} ranged from 671.28 to 672.60 hours after multiple dose administrations in subjects with FEM, and was independent of dose. Intersubject variability of $AUC_{0\text{-}\tau}$, $AUC_{0\text{-last}}$, and C_{max} was 42.9 to 66.9%. Mean concentration time profiles of ALD403 on Week 12 showed higher concentrations than those observed after the first dose administration (Day 0). The mean accumulation ratio based on $AUC_{0\text{-}\tau}$ [ARAUC] and C_{max} [ARC_{max}] across 30-mg and 300-mg dose levels ranged from 1.376 to 1.628 and from 1.384 to 1.553, respectively.

Safety Results: In this study, subjects were randomized equally to 1 of 4 treatment groups that included 3 dose strengths of ALD403 (ALD403 300 mg, 100 mg, 30 mg) and placebo. The majority of subjects within each dose group received all 4 infusions (retention averaged 91% for the second dose and approximately 80% for the third and fourth doses).

Overall, 530 subjects (59.7%) had at least one TEAE, and 103 subjects (11.6%) had at least one TEAE that was considered related to study drug. The incidence of TEAEs was generally balanced among treatment groups and no dose-related trends in incidence of TEAEs were observed. Overall, 25 subjects (2.8%) had a severe TEAE and 17 subjects (1.9%) had a serious TEAE. The incidence of severe and serious TEAEs was balanced among treatment groups. There were 29 subjects (3.3%) with a TEAE that led to study drug withdrawal with the highest incidence of TEAE leading to study drug withdrawal in the ALD403 30-mg group (12 subjects [5.5%]). Nineteen subjects (2.1%) had a TEAE leading to study drug interruption. There were no deaths reported.

The most frequently reported TEAEs by PT in ≥2% of subjects were upper respiratory tract infection (86 subjects [9.7%]), nasopharyngitis (57 subjects [6.4%]) and sinusitis (38 subjects [4.3%]).

Overall, 76 subjects (8.6%) had a TEAE of special interest (61 subjects [9.2%] in all ALD403 groups and 15 subjects [6.8%] in the placebo group). The number of treatment-emergent AESIs was balanced between the ALD403 groups and was slightly higher than the number of treatment-emergent AESI in the placebo group. The most frequently reported treatment-emergent AESIs by PT were infusion site extravasation (14 subjects [1.6%]), blood pressure increased (9 subjects [1.0%]), hypersensitivity (7 subjects [<1%]) followed by alanine aminotransferase increased, hypertension, palpitations and pruritus (5 subjects [<1%] each). All 11 subjects with treatment-emergent AESIs leading to study drug withdrawal were in an ALD403 treatment group, and 7 of these 11 subjects had events coded to the PT of hypersensitivity. Overall, numbers (%) of subjects

with events having a PT of hypersensitivity were low in the ALD403 treatment groups and no dose response was identified, 3 (<1%), 1 (<1%), and 4 (1.8%) in the 300-mg, 100-mg, and 30-mg groups, respectively. All events of hypersensitivity occurred during the time of infusion, were mild or moderate in severity, and either resolved without treatment or were effectively managed with standard medical treatment. Events of hypersensitivity did not occur in the placebo-treated group.

Throughout the study, no clinically concerning trends in clinical laboratory, vital signs or ECG results were identified; nor was any dose-response trend identified. There were no QTcF >500 msec values reported and values between 450 and 500 msec were few and transient.

A dose-response trend in the number of subjects with ADA positive results was observed after Week 8, and by Week 16 through Week 24 the incidence of ADA positive results was similar across the 300-mg and 100-mg groups. The ADA titers were low across all dose groups with no trend of increasing titer related to dose. The number of subjects with positive ADA results increased over time up to Week 24 and then decreased at timepoints after Week 24 to the end of study. Approximately 6% (29/512) of subjects who developed ADA remained positive at Week 56 (end of study). Characterization of the epitope specificity shows approximately 73% (351/482) of the ADA positive responses are predominately directed toward the complementarity determining regions (CDRs) of ALD403 and less than 4% (16/482) are directed toward the antibody framework. End of study (post Week 56) immunogenicity follow-up assessments at approximately 3- and 6-month timepoints are in process with final data to be reported in an addendum to the clinical study report.

Conclusions: ALD403 administered every 12 weeks by IV infusion for the preventive treatment of migraine in subjects with episodic migraine demonstrated a favorable benefit-risk profile for up to 1 year in Study ALD403-CLIN-006. The pharmacokinetics of ALD403 was predictable and consistent across doses and days. Increases in exposure were proportional to increases in dose and steady state was achieved by Week 12. The clinical study results show that ALD403 is associated with a statistically significant and clinically meaningful migraine preventive effect over multiple efficacy measures. A robust and meaningful migraine preventive effect was observed as early as the day after the first dose and was on average sustained over the initial and subsequent 12-week dosing intervals of 4 total doses. The most consistent efficacy profile was demonstrated for the ALD403 300--mg dose across multiple endpoints. The ALD403 100-mg dose also demonstrated efficacy for the primary efficacy endpoint. There were no meaningful differences observed in the safety profiles across the ALD403 dose groups. A single dose of ALD403 300 mg administered by IV infusion provided clinically meaningful and statistically superior efficacy over placebo in reduction of migraine days that was evident on the day following the first infusion and was maintained through 12 weeks. The therapeutic effects observed after the initial dose were maintained or improved with subsequent quarterly infusions. In addition to the reductions in migraine frequency, ALD403 treatment was associated with improvements

in measures of health-related quality-of-life. Taken together, ALD403 administered by IV infusion every 12 weeks was associated with a significant and clinically meaningful profile for effectiveness in the preventive treatment of migraine in adults with episodic migraine.

Date of Report: 26 July 2018